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(54) Title: PREVENTION OF POSTERIOR CAPSULAR OPACIFICATION BY ENDOCAPSULAR CIRCULATION OF CHEMICAL AGENTS

(57) Abstract:

PREVENTION OF POSTERIOR CAPSULAR OPACIFICATION BY ENDOCAPSULAR CIRCULATION OF CHEMICAL AGENTS

Field of the Invention

The present invention relates to a method of introducing chemical agents into an eye to treat an eye's lens capsule or cells therein for the purpose of preventing residual lens epithelial cell proliferation and posterior capsular opacification (PCO) or secondary cataract formation following extracapsular extraction of a cataractous lens. More particularly, the present invention is directed to using a relatively small capsulorhexis for cataractous lens removal to enable isolation of the lens capsule interior from the eye's anterior chamber. By isolating the lens capsule interior from the eye's anterior chamber, any number of chemical agents may be introduced into the lens capsule interior without exposing and harming tissues of the anterior chamber.

Background of the Invention

Cataract extraction is among the most commonly performed operations in the United States and the world. A cataractous lens is located within a capsular sac or lens capsule in an eye's posterior chamber. In order to gain access to the cataractous lens, an incision is typically made at the limbus of the eye for the purpose of introducing a surgical instrument into the

anterior chamber of the eye. In the case of extracapsular cataract extraction, a capsulorhexis procedure is performed in which a portion of the anterior membrane of the lens capsule adjacent to the iris is removed using a surgical instrument in order to provide direct access to the cataractous lens from the anterior chamber. The opacified lens is then removed through various known methods, including phacoemulsification. Phacoemulsification is a procedure entailing the application of ultrasonic energy to the lens in order to break the cataractous lens into small pieces that can be aspirated from the lens capsule. With the exception of the portion of the anterior membrane of the lens capsule removed during the capsulorhexis procedure, the lens capsule remains substantially intact throughout an extracapsular cataract extraction. Following removal of the cataractous lens (aphakia), an artificial intraocular lens (IOL) implant is typically implanted within the lens capsule in order to mimic the refractive function of a natural lens.

Although cataractous lens removal with IOL implant replacement provides significant benefits to most cataract patients, it is estimated that up to fifty percent (50%) of all patients who have IOL implants placed within the lens capsule will develop posterior capsular opacification (PCO) or secondary cataract within five years after surgery. PCO is caused by obstruction of optical zones by a deposit of cells and fibers on the posterior capsule or the IOL implant. Cell deposits on the posterior capsule and the IOL implant originate from the proliferation of residual lens epithelial cells on the interior surface of the lens capsule and from the accumulation of inflammatory cells and proteins. Of these two sources, the major cause of

PCO is the proliferation and migration of residual lens epithelial cells on the capsule membrane.

Ophthalmic surgeons, aware of the problems associated with residual lens epithelial cells, typically take considerable care in trying to remove all lens epithelial cells prior to implantation of an IOL implant. However, despite these efforts, a significant number of lens epithelial cells usually are left on the interior surface of the lens capsule. Lens epithelial cells are often left in the lens capsule since these cells are difficult to view and are often difficult to reach within the lens capsule.

The most common treatment for PCO entails the application of laser energy to the posterior membrane of the lens capsule for the purpose of creating an opening in the posterior capsule. However, the laser energy applied to the posterior membrane of the lens capsule is ordinarily directed through the IOL implant possibly resulting in damage to the optical and/or structural characteristics of the IOL implant. The application of laser energy to the posterior membrane of the lens capsule by design results in the destruction of a portion of the lens capsule as well. The destruction of a portion of the lens capsule creates risks from exposure of tissues to the vitreous, possibly resulting in serious or irreparable damage to the eye, such as an increase in intraocular pressure, retinal detachment and cystoid macular edema. Accordingly, it is preferable to prevent the occurrence of PCO rather than attempt to treat it at a later date through the application of laser energy.

Various procedures for the prevention of PCO have been suggested in recent years. Many such procedures have included the application of chemicals to the interior surface of the lens capsule in order to destroy residual lens epithelial cells. However, few if any of these procedures have proven to be particularly successful in the prevention of PCO due to the fact that it is extremely difficult to destroy residual lens epithelial cells without simultaneously destroying other cells within the eye, such as for example the corneal endothelium which does not regenerate. Selective destruction of residual lens epithelial cells by exploitation of the cells' increased proliferative activity has thus been the primary approach to the prevention of PCO.

Antimetabolites such as 5-fluorouracil (5FU) and daunomycin have been injected into the lens capsules of eyes in an attempt to prevent PCO. However, for antimetabolite therapy to be effective, the agents must be present when the residual lens epithelial cell proliferation resumes at an indeterminate time following surgery. Sustained drug delivery systems have also been investigated as a means for preventing PCO. However, the effective time frame within which to apply these agents may likewise be difficult to determine. Timing is difficult in the prevention of PCO since PCO is believed to result primarily from the propagation of residual lens epithelial cells of the germinal layer. These cells eventually proliferate and migrate across the lens capsule into the optical zone. To accurately predict the timing of such an event in order to destroy the cells and prevent cellular migration is difficult.

Immunotoxins, which are hybrid molecules composed of monoclonal antibodies chemically linked to toxic moieties, have also been used in the selective destruction of residual lens epithelial cells. The monoclonal antibody directs the toxic moiety to the target cell. The cell then internalizes the immunotoxin, thereby causing the vital biological processes of the cell to be compromised by the toxic moiety. Other efforts have been made to destroy residual lens epithelial cells. One such effort included the use of a fibroblastic growth factor bonded to a toxic moiety. However, monoclonal antibodies and fibroblastic growth factors are relatively expensive and difficult to produce on a reliable and consistent basis. Therefore, it is desirable to employ a method that provides selective destruction of residual lens epithelial cells without the costs and problems associated with monoclonal antibodies and growth factors.

Accordingly, a long felt need exists for a relatively simple, reliable and cost effective method of preventing posterior capsular opacification or secondary cataract in cataract patients.

Brief Summary of the Invention

Posterior capsular opacification (PCO) is believed to originate from lens epithelial cells of the germinal layer. These cells eventually proliferate and migrate across the lens capsule into the optical zone and obscure vision. Any number of chemical agents may be used to kill residual lens epithelial cells. However, chemical agents that will kill residual lens epithelial cells may also effect other cells within the eye, such as those of the eye's

anterior chamber. For example, chemical agents that will destroy residual lens epithelial cells, may also destroy corneal endothelial cells and cells of the iris if allowed to contact the same in the anterior chamber. The method of introducing toxic agents to the interior lens capsule of an aphakic eye in accordance with the present invention, is achieved by using a small incision and a relatively small capsulorhexis in the removal of a cataractous lens from an eye. By removing a cataractous lens through a relatively small capsulorhexis, chemical agents may be introduced into the lens capsule via a surgical instrument or cannula that forms a removable fluid-blocking seal with the lens capsule tissue edge formed by the capsulorhexis procedure. Introducing chemical agents through a removably sealed instrument or cannula allows for treatment of the lens capsule interior without exposing surrounding cells of the eye's anterior chamber. Chemical agents introduced into the lens capsule in accordance with the present method may lyse epithelial cell walls or be endocytosed into the proliferating cells. Cellular uptake or endocytosis may cause cellular death by inhibition of protein or nuclear acid synthesis or by inhibition of cellular metabolism. Another mechanism of cell distruction may be to disrupt cellular attachment to the lens capsule. Cells detached from the lens capsule would either die or be removed during irrigation and aspiration procedures. Thus, the method of the present invention prevents lens epithelial cell proliferation and PCO or secondary cataract formation following the extracapsular extraction of a cataractous lens.

Accordingly, it is an object of the present invention to provide a method of treatment for a lens capsule useful in the prevention of PCO.

Another object of the present invention is to provide a method of treatment for a lens capsule useful in the prevention of PCO, which is reliable and cost effective.

Another object of the present invention is to provide a method of treating a lens capsule with a cytotoxic concentration of a commonly available chemical agent.

Another object of the present invention is to provide a method of chemical treatment for a lens capsule useful in the prevention of PCO.

Another object of the present invention is to provide a safe method of chemical treatment for a lens capsule useful to prevent PCO.

Another object of the present invention is to provide a method of treating a lens capsule that is effective in destroying residual lens epithelial cells in an eye.

Still another object of the present invention is to provide a method of treating a lens capsule that specifically destroys residual lens epithelial cells in an eye.

These and other objectives and advantages of the present invention, some of which are specifically described and others that are not, will become apparent from the detailed description, examples and claims that follow.

Detailed Description of the Invention

The method of the present invention is intended to be used in an eye following endocapsular cataract extraction to non-specifically or specifically destroy residual lens epithelial cells disposed on an interior surface of the aphakic eye's lens capsule. The subject method may also be used in an eye following endocapsular cataract extraction to lyse cell walls and/or disrupt cell attachment to the lens capsule. By destroying residual lens epithelial cells disposed on the interior surface of the lens capsule by whatever means, the cells are prevented from proliferating and/or migrating along or across the surface of the lens capsule. The prevention of cellular proliferation and/or migration prevents opacification of the optic zone commonly referred to as posterior capsular opacification (PCO). The preferred method of the present invention is performed using an impeller probe equipped with a high-speed impeller interfaced with irrigation and aspiration capabilities as described in U.S. Patent Nos. 5,437,678 and 5,690,641, each incorporated herein in its entirety by reference. However, alternative surgical lens removal instruments may be used.

The preferred method of the present invention provides for an endocapsular cataract extraction to be performed by forming a relatively small, approximately 1.0 to 3.0 mm but preferably approximately 1.5 mm, incision is made in an eye in order to provide direct access to the anterior chamber of the eye. Although the necessary incision is usually formed at the limbus of the eye, it will be appreciated that alternative locations for this

incision may be selected at the discretion of the surgeon. Following the formation of the incision and expansion of the anterior chamber with a viscoelastic substance, a diathermy probe capable of burning a 1.0 to 1.5 mm diameter hole is activated upon the outer surface of the lens capsule. The hole created by the diathermy probe is used to perform a relatively small, approximately 1.0 mm to 3.0 mm or smaller, capsulorhexis procedure. After the capsulorhexis, the tip of an impeller probe is introduced through the relatively small capsulorhexis and into the lens capsule of the eye. The diameter of the impeller probe, approximately 1.5 mm to 3.5 mm or smaller, is slightly larger than that of the capsulorhexis. Accordingly, due to the small size of the capsulorhexis, a secure and removable fluid-blocking seal is formed between the lens capsule tissue edge formed by the capsulorhexis procedure and the impeller probe upon introduction thereof through the relatively small capsulorhexis. The impeller probe, equipped with a high-speed impeller, is capable of creating a high-speed vortex within the lens capsule when activated. The high-speed vortex created within the lens capsule brings the cataractous lens tissue to the high-speed impeller where the material is pulverized and removed via the impeller probe's irrigation and aspiration features. Alternatively, phacoemulsification techniques may be used to remove the cataractous lens. After or during removal of the cataractous lens from the lens capsule using the impeller probe, or similar technique, one or more chemical agents may be introduced into the lens capsule via the impeller probe's irrigation and aspiration feature. As an alternative method, the impeller probe or like lens removing device may be

removed from the lens capsule following lens removal and replaced by a cannula of similar diameter or approximately 0.1 to 1.0 mm larger diameter so as to provide a secure, removable fluid-blocking seal with the lens capsule capsulorhexis tissue edge. One or more chemical agents may then be introduced into the lens capsule via the cannula using an irrigation and aspiration system or the like. Using either method, after a predetermined period of time no longer than five minutes, remaining chemical agents may be removed from lens capsule by irrigating the same with a balanced salt solution. Chemical agents introduced into the lens capsule as described above destroy lens epithelial cells preventing the proliferation of such cells and thereby preventing PCO or secondary cataract formation following endocapsular extraction of a cataractous lens.

Suitable chemical agents for use in the present invention include agents that destroy lens epithelial cells on contact such as but not limited to surfactants, for example sodium dodecylsulfate (SDS) and polyoxyethylene sorbitan fatty acid ester (Tween), and hypotonic solutions, for example pure water. Surfactants and hypotonic solutions destroy lens epithelial cells by rupturing the cell membrane wall. Chemical and enzymatic agents that release lens epithelial cells from the lens capsule membrane are also suitable for use in the present invention. Such agents include ethylenediaminetetraacetic acid (EDTA), trypsin, disintegrins, arginine-glycine-asparagine (RGD) peptide analogs as well as antibodies directed against cell attachment receptors. Toxins that are internalized by lens epithelial cells and work by disruption of vital cellular processes are also

suitable for use in the present invention. Such toxins include mitomycin-C and saporin. Basement membrane binding agents conjugated to cytotoxic agents are likewise suitable. The conjugated basement membrane binding agents bond with basement membranes within the lens capsule. Because residual lens epithelial cells are disposed on the basement membranes within the lens capsule, the basement membrane binding agents when bonded to the basement membranes are in direct contact with the lens epithelial cells. The cytotoxic agents conjugated with the basement membrane binding agents are thereby present to destroy any migrating or proliferating lens epithelial cells. The lens epithelial cells internalize the cytotoxic agent, thereby destroying the cells on the interior surface of the lens capsule and thus preventing PCO. The basement membrane binding agent conjugated with the cytotoxic agent may be introduced within the lens capsule as described above and retained within the lens capsule for a predetermined period of time sufficient to permit the basement membrane binding agent to bond with the basement membranes within the lens capsule, such as for example one to five minutes. It will be appreciated that the length of time required for bonding the basement membrane binding agent to the basement membranes within the lens capsule is dependent upon a number of factors, including but not limited to, the concentration of the conjugated agent solution introduced into the lens capsule, the specific basement membrane binding agent selected and the irrigation techniques utilized in introducing the conjugated agent. Although it may not be necessary to contain membrane binding agents in the lens capsule as is true

with other chemical agents noted herein. However, containing the conjugated agent within the lens capsule does provide an additional level of safety to prevent the cytotoxic agents from binding basement membranes that may have been exposed during surgical trauma.

Suitable basement membrane binding agents for use in the present invention include for example but are not limited to poly-L-lysine and poly-D-lysine, but preferably poly-L-lysine due to its ready availability and relatively low cost. For purposes of simplicity, poly-L-lysine and poly-D-lysine are each hereinafter referred to indiscriminately as "polylysine". Other suitable basement membrane binding agents include but are not limited to fibronectin, laminin, type I, II, III and IV collagen, thrombospondin, vitronectin, polyarginine and platelet factor IV.

In accordance with the present invention one or more, but preferably one for purposes of simplicity, suitable basement membrane binding agents are conjugated with one or more, but preferably one for purposes of simplicity, cytotoxic agents. Suitable cytotoxic agents include ribosomal inhibitory proteins such as for example but not limited to saporin and ricin. Ribosomal inhibitory proteins are preferable in the present invention due to the fact that such proteins contain more inhibitory activity per microgram than other cytotoxic agents that can be used in connection with the method of the present invention. Other cytotoxic agents believed to be efficacious when used in connection with the present invention include, but are not limited to, antimitotic drugs such as methotrexate, 5-fluorouracil,

daunomycin, doxorubicin, mitoxanthrone, vinca alkaloids, vinblastine, colchicine, and cytochasins, and ionophores such as monensin and ouabain.

A variety of known methods can be employed for conjugating the cytotoxic agent, most preferably saporin, to the carbohydrate binding agent, most preferably polylysine. For example, the carboxyl groups of the cytotoxic agent can be bonded to the amines of the carbohydrate binding agent using a water-soluble carbodiimide technique. When this technique for conjugation is used, the entire conjugate will be internalized by the residual lens epithelial cells and degraded by the cell to release the cytotoxic agent.

Hetero-bi-functional cross-linkers such as (N-succinimidyl 3-[2-pyridyldithio]propionate (SPDP) also can be used to conjugate the cytotoxic agent to the carbohydrate binding agent, thereby creating a disulfide bond between the cytotoxic agent and the carbohydrate binding agent. By way of example and not by way of limitation, a conjugate of polylysine and saporin was prepared by coupling polylysine to SPDP as described in more detail in the examples provided below. The free SPDP was then removed using filtration technique or, in the alternative, through the use of a sepharose heparin column. The resulting polylysine-SPDP was then reduced with dithiothreitol. Saporin was then coupled with SPDP in the same manner and added to the solution of polylysine-SPDP. The resulting solution was filtered to remove uncoupled agents, thereby producing a conjugated polylysine-saporin solution.

The methods of the present invention for the prevention of PCO are described in still greater detail in the Examples that follow.

EXAMPLE 1: Surfactant destruction of lens epithelial cells

A 1.7 mm incision is made in an eye having a cataractous natural lens. A 2.2 mm capsulorhexis is performed on the anterior of the eye's lens capsule. During the removal of the cataractous natural lens material using phacoemulsification technique, the interior lens capsule is irrigated for 1 to 2 minutes with a 0.2% solution of SDS. The interior lens capsule is then irrigated for 1 to 2 minutes with a balanced salt solution.

EXAMPLE 2: Hypotonic solution destruction of lens epithelial cells

A 2.0 mm incision is made in an eye having a cataractous natural lens. A 3.0 mm capsulorhexis is performed on the anterior of the eye's lens capsule. During the removal of the cataractous natural lens material using a surgical probe equipped with an impeller, the interior lens capsule is irrigated for 1 to 5 minutes with pure water. The interior lens capsule is then irrigated for 1 to 2 minutes with a balanced salt solution.

EXAMPLE 3: Divalent cation chelator removal of lens epithelial cells

A 1.2 mm incision is made in an eye having a cataractous natural lens. A 2.0 mm capsulorhexis is performed on the anterior of the eye's lens capsule. After the removal of the cataractous natural lens material using phacoemulsification technique, the interior lens capsule is irrigated for 1 to 5

minutes with a 1 mg/ml solution of EDTA. The interior lens capsule is then irrigated for 1 to 2 minutes with a balanced salt solution.

EXAMPLE 4: Enzymatic removal of lens epithelial cells

A 1.5 mm incision is made in an eye having a cataractous natural lens. A 2.8 mm capsulorhexis is performed on the anterior of the eye's lens capsule. During the removal of the cataractous natural lens material using a surgical probe equipped with an impeller, the interior lens capsule is irrigated for 1 to 5 minutes with a 1 mg/ml solution of EDTA and 1mg/ml trypsin. The interior lens capsule is then irrigated for 1 to 2 minutes with a balanced salt solution.

EXAMPLE 5: Lens capsule detachment of lens epithelial cells

A 2.0 mm incision is made in an eye having a cataractous natural lens. A 2.8 mm capsulorhexis is performed on the anterior of the eye's lens capsule. During the removal of the cataractous natural lens material using a surgical probe equipped with an impeller, the interior lens capsule is irrigated for 1 to 5 minutes with a 10 mg/ml solution of RGD peptide analogs. The interior lens capsule is then irrigated for 1 to 2 minutes with a balanced salt solution.

EXAMPLE 6: Specific cytotoxic destruction of lens epithelial cells

Saporin was conjugated to polylysine using (N-succinimidyl 3-[2-pyridyldithio]propionate (SPDP) according to instructions provided by Pierce

Chemical Company, Rockford, Illinois. SPDP in 1.5M excess was allowed to react with saporin and polylysine individually to generate sulfhydryl groups on each component. Polylysine-SPDP was then treated with dithiothreitol and allowed to react with saporin-SPDP resulting in a disulfide linkage between the two species. The molar ratio of saporin to polylysine in the conjugate was the two species. The molar ratio of saporin to polylysine in the conjugate was calculated to be 1:1. The polylysine-saporin conjugate (PLS) was isolated from the free components by heparin sepharose chromatography. Molecular weight analysis was performed using sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). As expected, there was an apparent increase in molecular weight after conjugation to polylysine. Under non-reducing conditions PLS migrates as 2 bands with estimated molecular weights of 43,000 and 66,000 kD. The lower molecular weight band represents a conjugate of 1 polylysine + 1 saporin molecule and the higher molecular weight band represents a conjugate of 1 polylysine + 2 saporin molecules. In support of this, when PLS is run under reducing conditions, only one band results which migrates with free saporin. Polylysine is not visible with Coomassie blue staining. PLS was quantitated using the Lowry method for protein determination.

A 1.7 mm incision is made in an eye having a cataractous natural lens. A 2.2 mm capsulorhexis is performed on the anterior of the eye's lens capsule. During the removal of the cataractous natural lens material using a surgical probe equipped with a high speed impeller, the interior lens capsule is irrigated for 1 to 2 minutes with a 25 ug/ml solution of polylysine-saporin.

The interior lens capsule is then irrigated for 1 to 2 minutes with a balanced salt solution.

EXAMPLE 7: Internalized toxin destruction of lens epithelial cells

A 1.7 mm incision is made in an eye having a cataractous natural lens. A 2.2 mm capsulorhexis is performed on the anterior of the eye's lens capsule. During the removal of the cataractous natural lens material using phacoemulsification technique, the interior lens capsule is irrigated for 1 to 2 minutes with a 25 ug/ml solution of mitomycin-C. The interior lens capsule is then irrigated for 1 to 2 minutes with a balanced salt solution.

Following chemical agent treatment of the lens capsule, an intraocular lens (IOL) implant is implanted in the lens capsule. Such surgical method of implanting an IOL implant in an eye to replace a cataractous natural lens is well known to those skilled in the art as described in U.S. Patent Nos. 4,955,889 and 4,957,505, each incorporated herein in its entirety by reference.

Suitable IOL implants for use in the method of the present invention may be manufactured in any form acceptable for the intended purpose of replacing a cataractous natural lens as known to those skilled in the art. The lens may be formed in a plate-style configuration as described in U.S. Patent Nos. 4,664,666 and 4,936,850, each incorporated herein in its entirety by reference, or formed in a haptic-style configuration as described in U.S. Patent Nos.4,822,358, 4,842,600 and 4,863,464, each incorporated herein

in its entirety by reference. However, either lens configuration is equally suitable for the present invention.

Suitable IOL implants may be formed from any acceptable material known to those skilled in the art such as polymethylmethacrylate (PMMA), silicone, acrylates, hydrogels or a combination thereof.

As described above, the method of the present invention provides an effective treatment to prevent PCO in cataract patients. The present description of the subject method is provided for purposes of illustration and explanation. It will be apparent to those skilled in the art that modifications and changes may be made to the described method without departing from its scope and spirit.

We claim:

1. A method of preventing posterior capsular opacification comprising:

creating an incision within an eye and a relatively small capsulorhexis in a lens capsule of said eye;

inserting at least a portion of a lens removal instrument in said capsulorhexis to form a removable seal between said instrument and said capsulorhexis;

activating said instrument to remove a natural lens; and

introducing one or more chemical agents within said lens capsule

using said instrument or a cannula removably sealed with said capsulorhexis.

2. A method of implanting an intraocular lens implant within an eye to prevent posterior capsular opacification comprising:

creating an incision in an eye and a relatively small capsulorhexis within a lens capsule of said eye;

removing a natural lens from said lens capsule of said eye using a lens removal instrument;

introducing one or more chemical agents into said lens capsule through said lens removal instrument or a cannula removably sealed with said capsulorhexis; and

implanting a lens implant within said lens capsule.

3. A method of treating a lens capsule of an eye to prevent posterior capsular opacification comprising:

creating a relatively small capsulorhexis in a lens capsule of an eye;

inserting at least a portion of a lens removal instrument within said lens capsule to remove a natural lens from said lens capsule;

introducing one or more chemical agents within said lens capsule using said instrument or a cannula removably sealed with said capsulorhexis; and

implanting a lens implant within said lens capsule.

4. A method of destroying residual lens epithelial cells within a lens capsule of an eye comprising:

inserting at least a portion of a lens removal instrument within a lens capsule forming a seal therewith; and

introducing one or more chemical agents within said lens capsule using irrigation and aspiration capabilities of said instrument.

5. The method of claim 2 or 3 wherein said implant is manufactured from one or more materials selected from the group consisting of polymethylmethacrylate, silicone, acrylate and hydrogel.

6. The method of claim 2 or 3 wherein said implant is manufactured from a hydrogel material.

7. The method of claim 2 or 3 wherein said implant is manufactured in a plate configuration or a haptic configuration.

8. The method of claim 1, 2, 3 or 4 wherein said one or more chemical agents includes one or more basement membrane binding agents conjugated to one or more cytotoxic agents.

9. The method of claim 1, 2, 3 or 4 wherein said one or more chemical agents includes one or more basement membrane binding agents conjugated to one or more cytotoxic agents selected from the group consisting of ribosomal inhibitory proteins, antimitotic drugs and ionophores.

10. The method of claim 1, 2, 3 or 4 wherein said one or more chemical agents includes one or more basement membrane binding agents selected from the group consisting of poly-L-lysine, poly-D-lysine, fibronectin, laminin, type I, II, III or IV collagen, thrombospondin, vitronectin, polyarginine and platelet factor IV, conjugated to one or more cytotoxic agents.

11. The method of claim 1, 2, 3 or 4 wherein said one or more chemical agents includes poly-L-lysine or poly-D-lysine as a basement membrane binding agent conjugated to one or more cytotoxic agents.

12. The method of claim 1, 2, 3 or 4 wherein said one or more chemical agents includes one or more cytotoxic agents selected from the group consisting of ribosomal inhibitory proteins, antimitotic drugs and ionophores.

13. The method of claim 1, 2, 3 or 4 wherein said one or more chemical agents include one or more ribosomal inhibitory proteins as cytotoxic agents.

14. The method of claim 1, 2, 3 or 4 wherein said one or more chemical agents include one or more cytotoxic agents selected from the group consisting of saporin, ricin, methotrexate, 5-fluorouracil, daunomycin, doxorubicin, mitoxanthrone, vinca alkaloids, vinblastine, colchicine, cytochasins, monensin and ouabain.

15. The method of claim 1, 2, 3 or 4 wherein said one or more chemical agents include the cytotoxic agent saporin.

16. The method of claim 1, 2, 3 or 4 wherein said one or more chemical agents includes one or more basement membrane binding agents conjugated to one or more cytotoxic agents using (N-succinimidyl 3-[2-pyridyldithio]propionate).

17. The method of claim 1, 2, 3, or 4 wherein said one or more chemical agents is a surfactant.

18. The method of claim 1, 2, 3, or 4 wherein said one or more chemical agents is a hypotonic solution.

19. The method of claim 1, 2, 3, or 4 wherein said one or more chemical agents is a divalent cation chelator.

20. The method of claim 1, 2, 3, or 4 wherein said one or more chemical agents is an analog or antibody directed against cell attachment receptors.

PATENT COOPERATION TREATY

PCT

DECLARATION OF NON-ESTABLISHMENT OF INTERNATIONAL SEARCH ~~REPORT~~

(PCT Article 17(2)(a), Rules 13ter.1(c) and Rule 39)

Applicant's or agent's file reference	IMPORTANT DECLARATION	Date of mailing (day/month/year)
P02793-PCT		18/01/2002
International application No.	International filing date (day/month/year)	(Earliest) Priority date (day/month/year)
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International Patent Classification (IPC) or both national classification and IPC	A61F9/007, A61L27/34 A61L27/54, A61K9/00	
Applicant		
BAUSCH & LOMB SURGICAL, INC.		

This International Searching Authority hereby declares, according to Article 17(2)(a), that **no International search report will be established** on the International application for the reasons indicated below

1. [X] The subject matter of the International application relates to:
   - a. [ ] scientific theories.
   - b. [ ] mathematical theories
   - c. [ ] plant varieties.
   - d. [ ] animal varieties.
   - e. [ ] essentially biological processes for the production of plants and animals, other than microbiological processes and the products of such processes.
   - f. [ ] schemes, rules or methods of doing business.
   - g. [ ] schemes, rules or methods of performing purely mental acts.
   - h. [ ] schemes, rules or methods of playing games.
   - i. [X] methods for treatment of the human body by surgery or therapy.
   - j. [X] methods for treatment of the animal body by surgery or therapy.
   - k. [ ] diagnostic methods practised on the human or animal body.
   - l. [ ] mere presentations of information.
   - m. [ ] computer programs for which this International Searching Authority is not equipped to search prior art.

2. [X] The failure of the following parts of the International application to comply with prescribed requirements prevents a meaningful search from being carried out:
   [ ] the description [X] the claims [ ] the drawings

3. [ ] The failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions prevents a meaningful search from being carried out:
   [ ] the written form has not been furnished or does not comply with the standard.
   [ ] the computer readable form has not been furnished or does not comply with the standard.

4. Further comments: see further information

Name and mailing address of the International Searching Authority	Authorized officer
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 203

A meaningful search is not possible on the basis of all claims because all claims are directed to - Method for treatment of the human or animal body by surgery - Rule 39.1(iv) PCT

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.